AP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: WATSON et al.	Confirmation No: 8178
Appl. No.	: 09/975,317	
Filed	: October 12, 2001	
Title	: METHOD	
TC/A.U.	: 1618	
Examiner	: D. L. Jones	
Docket No.:	: WATS3001C/REF	
Customer No:	: 23364	

APPEAL BRIEF UNDER 37 CFR §41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief on appeal is submitted without a further fee as the required fee of $500.00 under § 41.20(b)(2) for a large entity was previously submitted with the earlier submitted brief which was returned to the Examiner by the Board for further consideration. A new final rejection was issued and a new notice of appeal was filed on November 13, 2006. The period for filing the brief is set to expire on January 13, 2007. This appeal brief is timely filed.

However, to insure consideration of this brief, should further fees be necessary, any additional fees necessary for this appeal may be charged against the undersigned's Deposit Account No. 02-0200.

41.37 (c)(1)(i). REAL PARTY IN INTEREST

The real party in interest is GE HEALTHCARE AS.

41.37 (c)(1)(ii). RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal known to appellants, appellants' legal representative or assignee.

41.37 (c)(1)(iii). STATUS OF CLAIMS

This application contains 96 claims. Claims 1-75, 82, 83, 87, 94, and 95 have been canceled from the application without prejudice or disclaimer. Appellants reserve the right to file a further continuation application to any subject matter described and /or claimed in the application as originally filed which is not the subject of this appeal.

Claims 76-81, 84-86, 88-93 and 96 are pending in the application and have been finally rejected. Claims 76-81, 84-86, 88-93 and 96 are the claims on appeal.

41.37 (c)(1)(iv). STATUS OF AMENDMENTS

No amendment after final rejection has been filed. The claims on appeal are as finally rejected.

41.37 (c)(1)(v). SUMMARY OF CLAIMED SUBJECT MATTER

It has now surprisingly been found that substantially lower, clinically acceptable, dosages of manganese may be used in fast or ultra-fast imaging techniques to provide an effective method of myocardial imaging, in particular to provide important information

about myocardial viability during or following a severe heart attack or coronary occlusion. (Page 3 line 31 to page 4, line 4.)

Preferably, the method of the invention provides a method of functional imaging which may discriminate between normal tissue, reversibly and irreversibly injured tissue during ischemia and during reperfusion. In particular , the invention provides a means for discriminating between reversibly and irreversibly injured tissue. (Page 5, lines 5-11.)

The claimed invention thus provides a method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue, the method comprising administering to a body a physiologically acceptable manganese complex or salt thereof as defined by formula (I), within a period of from 3 to 6 hours following administration of said complex or salt thereof subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and distinguishing viable myocardial tissue from infarcted tissue. (Page 9, lines 10-20 and paragraph bridging pages 11 and 12.)

41.37 (c)(1)(vi). GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first ground of rejection to be reviewed on appeal is the rejection of claims 76, 77, 79-81, 84-86, 88-93 and 96 under 35 U.S.C. 103 as being prima facie obvious over Rocklage, U.S. Patent 5,190,744 in view of Rocklage, U. S. Patent 4,889,931.

The second and final ground of rejection to be reviewed on appeal is the rejection of claims 77, 78 and 96 as being prima facie obvious under 35 U.S.C. 103 over Rocklage, U.S. Patent 5,190,744 in view of Goldenberg, U. S. Patent 5,632,968.

41.37 (c)(1)(vii). ARGUMENT

THE OBVIOUSNESS REJECTIONS

The legal standard

With respect to an obviousness rejection, Appellants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

A. Claims 76, 77, 79-81, 84-86, 88-93 and 96 are not prima facie obvious under 35 USC 103(a) over Rocklage U.S. Patent 5,190,744 in view of Rocklage U. S. Patent 4,889,931

In the final rejection, it is urged that Rocklage '744 discloses a method of detecting myocardial ischemia in a subject comprising administering a contrast medium comprising a manganese complex and subjecting the subject to a fast MRI technique to detect abnormal blood flow. The specific support for this statement in the final rejection is a reference to see the Abstract of the cited patent. In the Abstract, the invention is said to be particularly useful in the determination of the extent and severity of ischemia. It does not refer to myocardial ischemia as stated in the final rejection and this statement is therefore specifically traversed.

The methods of Rocklage '744 are also said to be for imaging myocardial ischemia in the final rejection with reference to column 2, lines 33-38 and column 8, lines 17-57. However, column 2, lines 33-38 actually refers to cerebral or coronary ischemia and not myocardial ischemia as would be appreciated by one of ordinary skill in the art to which the invention pertains much less the claim limitation of a method of distinguishing viable myocardial tissue from necrotic tissue, a claim limitation which cannot be ignored. Similarly, column 8 lines 17-57 makes no mention of myocardial ischemia, but instead describes the use of DyDTPA, (not within formula I of claim 96) for measuring cerebral ischemia. Accordingly, these statements are specifically traversed and should be withdrawn and in no way support the obviousness rejection of the claimed subject matter. They do not provide the necessary motivation to modify the prior art to arrive at the presently claimed invention.

Claim 96 on appeal claims a method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or nonhuman body whereas Rocklage '744 is concerned with the detection of cerebral (brain) ischemia as is evident from the

detailed discussion and working examples contained in the patent. Although Rocklage '744 also teaches that the same method would be useful in the detection of coronary ischemia, the myocardium and coronary arteries are different parts of the heart - the myocardium is the middle muscular layer of the heart wall, and coronary arteries surround the heart and branch out from the aorta to supply blood to the heart as would be appreciated by one of ordinary skill in the art. There is no motivation in Rocklage '744 which suggests the claimed invention nor is there a suggestion of the likelihood of success in arriving at the presently claimed invention. Obvious to try is not the standard of obviousness under 35 USC 103. Moreover, the only suggestion of distinguishing myocardial tissue is in Appellants' specification which may not be used as a teaching reference. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.). Rocklage '744 does not therefore describe a method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or nonhuman body as in the presently claimed invention.

As noted, Rocklage '744 does not disclose a method of distinguishing between reversibly injured tissue and irreversibly injured tissue, a claim limitation which cannot be ignored. Rocklage describes only a method for detecting ischemia. Ischemia is a decrease of blood supply which leads to an inadequate supply of oxygen where the blood supply is limited as would be appreciated by one of ordinary skill in the art. Again, the necessary motivation to make this determination is not in the prior art but only in Appellants' disclosure which is not available as a teaching reference.

Independent claim 96 is directed to a method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue. Ischemia leads to the damage of tissue to which the patient's blood supply has been affected. The extent of the tissue damage within a patient can vary such that the damage to some tissue is reversible, whereas the damage to other tissue is not. Claim 96 is limited to a method for distinguishing between these

types of tissue following/during an ischemic event. Such a method is nowhere disclosed or suggested in Rocklage '744 as would be appreciated by one of ordinary skill in the art.

Claim 96 is limited in administering to the body a physiologically acceptable manganese complex wherein the manganese complex is a manganese chelate complex having a K_a value of from 10^7 to 10^{25} and a formula (I) or a salt thereof as specifically defined in the claim and at a dosage of 0.001 to 0.2 mmol/kg bodyweight. These are claim limitations which cannot be ignored.

The contrast agents described in Rocklage '744, in particular the Dy-compounds described in the Examples of '744, are blood pool agents and are detected in the blood supply by MRI as would be appreciated by one of ordinary skill in the art to which the invention pertains. As a result, the method described in Rocklage '744 can only be used to identify and/or monitor abnormal or modified blood flow. The method does not involve or allow for the detection of damaged tissue in accordance with the claims on appeal. Again, this is a limitation which cannot be ignored. The method claimed in the claims on appeal relies on the contrast agent used being able to distinguish between reversibly and irreversibly injured myocardial tissue. This correlation is neither taught nor suggested by the combination of references relied upon in the final rejection.

This is achieved using the contrast agents defined in the claims on appeal. The manganese contrast agents of the claimed invention dissociate once they have been administered into the body and the resulting manganese ions are able to enter viable (i.e. repairable) myocardial cells via Ca^{2+} channels. It should be noted that one of ordinary skill in the art would appreciate that not all metal ions are capable of being taken up by cells via Ca^{2+} channels. The manganese ions are not however able to enter myocardial cells which are irreversibly damaged. The manganese ions generate a signal in MRI imaging, thereby generating a signal in the viable myocardial cells. Since manganese ions cannot be taken up by irreversibly damaged cells, no such signal is generated in necrotic (infarcted) cells. There is no suggestion of this in the prior art relied upon in rejection of the claims on appeal.

As discussed at page 9 of Appellants' specification, the method of the present invention provides for the administration of the specified manganese complex and imaging within a period of from 3 to 6 hours after administration of the complex (delayed imaging). There is no suggestion of this time limitation in the '477 patent and this is a claim limitation which cannot be ignored. As pointed out by Applicants, the return of normal cardiac function following reversible ischemia leads to normalization of both cellular uptake and retention of manganese. Delayed imaging is used to identify viable myocardium after reopening of coronary arteries by PTCA or by fibrinolytic therapy which is not suggested by the teaching of the '477 patent to one of ordinary skill in the art. As stated in the paragraph bridging pages 8 and 9 of Applicants' specification, delayed imaging techniques in which imaging is carried out post injection have been found to be particularly effective in distinguishing infarcted from normal myocardium and in characterizing the severity of damage in the injured zone.

The method claimed in claim 96 on appeal is therefore able to distinguish between the two types of cells. It is the result of Appellants' teaching with respect to the specified dissociation constant, as specified in the claims, and the selection of the contrast agent of formula (I) as taught by Appellants and specified in the claims on appeal that the advantageous process of the present invention is obtained.

Appellants acknowledge that Rocklage '744 does refer to manganese ions. However, this reference forms part of the general teaching provided by the patent. It is recognized at the top of page 4 of the Official Action of July 16, 2004, that Rocklage '744 teaches that various known chelating agents may be employed in column 4, but fails to specifically disclose the use of the same contrast agents as instantly claimed (e.g., manganese complexes, such as, those of formula I of claim 96 and dosages thereof. The preference for the contrast agents is stated to be the lanthanide ions, especially high spin lanthanides such as ions of Dy, Gd, Eu and Ho, in particular Dy(III) as would be appreciated by one of ordinary skill in the art from a reading of the patent. This leads

one of ordinary skill in the art, away from the contrasts agents used in the presently claimed invention, when the teachings of the reference are viewed in their entirety.

It is acknowledged that Rocklage '744 mentions Mn as one of several possible metals but there is nothing to lead to this particular metal in place of Dy as the clear preference from the references disclosure. This choice appears to be clearly based on Appellants' disclosure and is the result of impermissible hindsight.

The Final Rejection attempts to overcome these deficiencies in Rocklage '744 by relying on the teachings of the reference to manganese chelates in Rocklage '931. This represents no more than an obvious to try standard of obviousness since Rocklage '744 does not disclose a method for distinguishing between reversibly and irreversibly injured myocardial tissue as discussed above and nor does Rocklage '931. In fact, this reliance appears to be based on hindsight reconstruction based on Appellants' teaching.

The level of one of ordinary skill in the art must be taken into consideration as well as the teachings of the reference as a whole. It should be noted that Dy-contrast agents are particularly preferred as noted at column 4 lines 1-7 of the '744 reference. This is a teaching away from the manganese contrast agents of the presently claimed invention. Only Dy-contrast agents are employed in the Examples of Rocklage '744, and Dy-contrast agents are not suitable for detecting the viability of myocardial cells. This is because Dy-contrast agents are taken up neither by viable myocardial cells nor by irreversibly damaged myocardial cells. Consequently, a method employing such contrast agents is not able to distinguish between the two types of cells in accordance with the presently claimed invention.

Moreover, Dy is the chemical symbol for Dysprosium which is an element of the lanthanide series and not a transition metal such as manganese used in the method of the present invention. Mn is included in the list of at column 4 but this requires a selection and again requires the improper application of hindsight or the obvious to try standard. Appellants note the Examiner's reference to claim 26 but this includes the

limitation from claim 1 and there is no support for the limited grouping identified in the claim in the specification.

Claim 96 also requires that within a period of from 3 to 6 hours following administration of the Mn complex or salt to the body, the body is subjected to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and distinguishing viable myocardial tissue from infarcted tissue; with the proviso that said manganese complex or salt thereof is the only contrast agent administered in the method. There is no discussion in the Final Rejection of where in the references relied upon in the rejection is the teaching for these additional limitations.

The method as claimed in claim 96 can therefore be distinguished from the methods described in the prior art. Furthermore, it is submitted that the claimed method is not obvious since a method for distinguishing reparable myocardial cells from irreparable cells is nowhere disclosed in the prior art. None of the prior art documents even address the problem of distinguishing reparable cells from irreparable cells. Furthermore, neither is there anything in the prior art to suggest that manganese contrast agents would dissociate when administered to a patient, nor that the resulting manganese ions would be taken up by viable myocardial tissue and not by necrotic tissue. The skilled person would not therefore be led to the claimed method from the cited prior art. Common knowledge and common sense of person of ordinary skill in the art is no good to reject under 35 USC 103(a); In re Lee 61 USPQ2d 1430 (CAFC 2002), teachings in the prior art are required.

Thus, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Rocklage '744 using the teachings of Rocklage '931 and generate a method of distinguishing viable myocardial tissue from necrotic (infracted) tissue in a subject as set forth in independent claim 96. Contrary to the assertion in the final rejection both references do not disclose the use of contrast agents for imaging the cardiovascular system. Rocklage '931 simply relates to the

preparation of an NMRI contrast agent. There is no specific disclosure of imaging the cardiovascular system in this patent. While it may be argued that the chelating agents disclosed by Rocklage '931 encompass those of the instant invention, there is no teaching which would lead one of ordinary skill in the art to substitute these agents for those described in Rocklage '744 and obtain the presently claimed invention. At most, there is a teaching of obvious to try the contrast agents of Rocklage '931 in the method of Rocklage '744 but there is no teaching of an expectation of arriving at the invention of the claims on appeal from the teachings of either reference, alone or in combination.

It is urged in the final rejection, without reference to any supporting documentation or sound scientific reasoning, that a skilled practitioner in the art would recognize that imaging the heart generates an image of the complete heart so while the entire heart will be imaged, the intensity of the contrast agent absorb would vary depending upon the type of tissue (i.e., nfarcted and/or healthy) present. There is no citation of any reference which contains this teaching. For example, it is urged that the skilled practitioner would recognize that the properties of infarct and healthy tissue are different so the outcome from administering a composition would differ such that while both tissues would be imaged, one would be able to distinguish between the two based on the intensity of absorbed contrast agent. Clearly, since there is no support for this argument, it is clearly based on improper hindsight and should be withdrawn. This clearly does not lead one of ordinary skill in the art to the method of the claims on appeal.

In addition, it is urged in the final rejection that since a skilled practitioner in the art would recognize that since the compositions administered to the subject are the same, the properties of those compositions would be the same as well. Thus, if Applicants' contrast agent is capable of distinguishing between viable and necrotic myocardial tissue, the contrast agents of the prior art would also possess those properties. Again, this argument is clearly based on Appellants' teaching and not a fair interpretation of the combined teachings of the prior art by one of ordinary skill in the art.

Furthermore, it is noted in the final rejection that in Rocklage '744, it is disclosed that MRI using magnetic susceptibility contrast agents allows one to determine the existence and location of a perfusion deficit (e.g. cerebral ischemia) and detect the degree or severity, and if possible the onset and duration, of abnormalities or variations in a quantifiable manner when a subject is administered a contrast agent (abstract, column 1, lines 7-12 and 26-55). The parenthetical statement with respect to cerebral ischemia was omitted from the statement in the final rejection. However, the teaching of the reference in no way teaches the subject matter of the claims on appeal as discussed above. Accordingly, it is most respectfully requested that this rejection be withdrawn or reversed on appeal.

B. Claims 77, 78 and 96 are not prima facie obvious under 35 USC 103(a) over Rocklage U.S. Patent 5,190,744 in view of Goldenberg U. S. Patent 5,632968

It is urged in the final rejection that Rocklage '744 discloses that "various varieties of echo planar imaging are suitable with their invention" in column 2, lines 19-23, but fails to specifically disclose that the echo imaging is an inversion recovery echo imaging method. It is then urged that Godenberg discloses methods of imaging cardiovascular lesions and teaches that inversion recovery is a well know and equivalent method of spin-echo MRI, with reference to column 13, lines 23-48 of the patent.

It is concluded in the final rejection that it would be obvious to one of ordinary skill in the art to further modify the methods disclosed by Rocklage '744 to use inversion-recovery spin-echo MRI as the spin echo MRI procedure because it is well known in the art that this is a useful and equivalent method of spin-echo MRI as taught by Goldenberg. Appellants' make no admission with respect the correctness of the Examiner's comments as stated in this rejection. However, this rejection is clearly

untenable for the reasons discussed above with respect to the prior rejection and should be withdrawn or reversed.

It is most respectfully submitted that the claim 78 is dependent on claim 77 which is dependent on claim 96, the sole independent claim on appeal.

As previously noted, claim 96 is limited administering to the body a physiologically acceptable manganese complex wherein the manganese complex is a manganese chelate complex having a K_a value of from 10^7 to 10^{25} and a formula (I) or a salt thereof as specifically defined in the claim and at a dosage of 0.001 to 0.2 mmol/kg bodyweight. These are claim limitations which cannot be ignored.

The contrast agents described in Rocklage '744, in particular the Dy-compounds described in the Examples of '744, are blood pool agents and are detected in the blood supply by MRI as would be appreciated by one of ordinary skill in the art to which the invention pertains. As a result, the method described in Rocklage '744 can only be used to identify and/or monitor abnormal or modified blood flow. The method does not involve or allow for the detection of damaged tissue in accordance with the claims on appeal.

The method claimed of the claims on appeal relies on the contrast agent used being able to distinguish between reversibly and irreversibly injured myocardial tissue. This is achieved using the contrast agents defined in the claims on appeal. The manganese contrast agents of the claimed invention dissociate once they have been administered into the body and the resulting manganese ions are able to enter viable (i.e. repairable) myocardial cells via Ca^{2+} channels. It should be noted that one of ordinary skill in the art would appreciate that not all metal ions are capable of being taken up by cells via Ca^{2+} channels. The manganese ions are not however able to enter myocardial cells which are irreversibly damaged. The manganese ions generate a signal in MRI imaging, thereby generating a signal in the viable myocardial cells. Since manganese ions cannot be taken up by irreversibly damaged cells, no such signal is generated in necrotic (infarcted) cells. The method claimed in present claim 96 is therefore able to distinguish between the two types of cells.

Appellants acknowledge that Rocklage '744 does refer to manganese ions. However, this reference forms part of the general teaching provided by the document. It is recognized that Rocklage '744 teaches that various known chelating agents may be employed in column 4, but fails to specifically disclose the use of the same contrast agents as instantly claimed (e.g., manganese complexes, such as, those of formula I of claim 96) and dosages thereof.

The Final Rejection attempts to overcome these deficiencies in Rocklage '744 by relying on the teachings of the reference to manganese chelates in Rocklage '931. This reference is not applied in the present rejection but even if it were, this represents no more than an obvious to try standard of obviousness since Rocklage '744 does not disclose a method for distinguishing between reversibly and irreversibly injured myocardial tissue as discussed above, and nor does Rocklage '931. The Goldenberg reference does not overcome this deficiency. Accordingly, this rejection does not render the claims obvious and should also be withdrawn or reversed on appeal.

CONCLUSION

In view of the above arguments, the rejections of the claims on appeal should not be sustained on appeal. The rejections should be reversed and the application passed to issue.

Respectfully submitted,
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41.37 (c)(1)(viii) Claims appendix

76. A method as claimed in claim 96 wherein said magnetic resonance imaging procedure is one capable of generating images with time intervals of less than 100 milliseconds.

77. A method as claimed in claim 96 wherein said imaging procedure is a gradient echo or echo planar imaging procedure.

78. A method as claimed in claim 77 wherein said imaging procedure is an inversion recovery echo planar imaging procedure.

79. A method as claimed in claim 77 wherein said imaging procedure is one in which TI (inversion time) is 100 to 800 msecs.

80. A method as claimed in claim 96 wherein said manganese complex or salt thereof is administered at a dosage of 0.005 to 0.2 mmol/kg bodyweight.

81. A method as claimed in claim 80 wherein said manganese complex or salt thereof is administered at a dosage of 0.01 to 0.05 mmol/kg bodyweight.

84. A method as claimed in claim 96 wherein in formula I:

R^5 is hydroxy, C_{1-8} alkoxy, ethylene glycol, glycerol, amino or C_{1-8} alkylamido;

X is a bond or a group selected from CH_2, $(CH_2)_2$, CO, CH_2CO, CH_2CH_2CO or CH_2COCH_2;

Y is a bond;

R^6 is a mono- or poly(hydroxy or alkoxylated) alkyl group or a group of the formula $OP(O)(OR^8)R^7$; and

R^7 is hydroxy or an unsubstituted alkyl or aminoalkyl group.

85. A method as claimed in claim 96 wherein in formula I, R^3 is ethylene and each group R^1 represents $-CH_2COR^5$ in which R^5 is hydroxy.

86. A method as claimed in claim 96 in which the compound of formula I is N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid (DPDP) or N,N'-dipyridoxyl-ethylenediamine-N,N'-diacetic acid (PLED).

88. A method as claimed in claim 96 wherein said magnetic resonance imaging procedure is carried out within a period of up to 6 hours after the administration of said complex or salt thereof to said body.

89. A method as claimed in claim 96 wherein the contrast medium further comprises calcium chelate complexes.

90. A method as claimed in claim 96 wherein the contrast medium further comprises calcium or sodium salts.

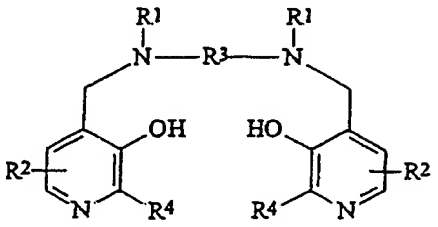
91. A method as claimed in claim 90 wherein the calcium salt comprises calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate.

92. A method as claimed in claim 96 wherein the contrast medium further comprises physiologically compatible buffers.

93. A method as claimed in claim 96 wherein the contrast medium further comprises an antioxidant such as ascorbic acid or a reducing sugar.

96. A method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or nonhuman body, said method comprising administering to said body a physiologically acceptable manganese complex wherein said manganese complex is a manganese chelate complex having a K_a value of from 10^7 to 10^{25} and a

formula I:



; (I)

or a salt thereof

(wherein in formula I

each R^1 independently represents hydrogen or $-CH_2COR^5$;

R^5 represents hydroxy, optionally hydroxylated alkoxy, amino or alkylamido;

each R^2 independently represents a group XYR^6;

X represents a bond, or a C_{1-3} alkylene or oxoalkylene group optionally substituted by a group R^7;

Y represents a bond, an oxygen atom or a group NR^6;

R^6 is a hydrogen atom, a group $COOR^8$, an alkyl, alkenyl, cycloalkyl, aryl or aralkyl group optionally substituted by one or more groups selected from $COOR^8$, $CONR^8_2$, NR^8_2, OR^8, $=NR^8$, =O, $OP(O)(OR^8)R^7$ and OSO_3M;

R^7 is hydroxy, an optionally hydroxylated, optionally alkoxylated alkyl or aminoalkyl group;

R^8 is a hydrogen atom or an optionally hydroxylated, optionally alkoxylated alkyl group;

M is a hydrogen atom or one equivalent of a physiologically tolerable cation;

R^3 represents a C_{1-8} alkylene group, a 1,2-cycloalkylene group, or a 1,2-arylene group; and

each R^4 independently represents hydrogen or C_{1-3} alkyl);

at a dosage of 0.001 to 0.2 mmol/kg bodyweight, within a period of from 3 to 6 hours following administration of said complex or salt thereof subjecting said body to a

magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and distinguishing viable myocardial tissue from infarcted tissue; with the proviso that said manganese complex or salt thereof is the only contrast agent administered in said method.

(ix) Evidence appendix

NONE

(X) Related proceedings appendix

NONE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: WATSON et al.	Confirmation No: 8178
Appl. No.	: 09/975,317	
Filed	: October 12, 2001	
Title	: METHOD	
TC/A.U.	: 1616	
Examiner	: D. L. Jones	
Docket No.:	: WATS3001C/REF	
Customer No:	: 23364	

INTERVIEW SUMMARY RECORD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the final rejection and takes into consideration the Interview conducted with Examiner Jones on December 28, 2006 in connection with the above-identified application. A notice of appeal was filed on November 13, 2006, making the appeal brief due on January 13, 2007. The appeal brief is filed concurrently herewith.

At the interview, the outstanding rejection in which it is urged that Rocklage '744 discloses a method of detecting myocardial ischemia in a subject comprising administering a contrast medium comprising a manganese complex and subjecting the subject to a fast MRI technique to detect abnormal blood flow was discussed. At the interview the Abstract of the cited patent was noted. In the Abstract, the invention is said to be particularly useful in the determination of the extent and severity of ischemia. It does not refer to myocardial ischemia as stated in the final rejection. Moreover, it was noted at the interview that at column 2 of the patent, lines 34 and 35, the reference is to cerebral or coronary ischemia. This does not suggest to one of ordinary skill in the art the presently claimed invention which is to a method of distinguishing viable myocardial tissue from necrotic tissue.

Similarly, column 8 lines 17-57 makes no mention of myocardial ischemia, but instead describes the use of DyDTPA, (not within formula I of claim 96) for measuring cerebral ischemia.

Claim 96 claims a method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or nonhuman body whereas Rocklage '744 is concerned with the detection of cerebral (brain) ischemia as is evident from the detailed discussion and working examples contained in the patent. Although Rocklage '744 also teaches that the same method would be useful in the detection of coronary ischemia, it was pointed out that the myocardium and coronary arteries are different parts of the heart - the myocardium is the middle muscular layer of the heart wall, and coronary arteries surround the heart and branch out from the aorta to supply blood to the heart as would be appreciated by one of ordinary skill in the art.

It was noted at the interview that there is no motivation in Rocklage '744 which suggests the claimed invention nor is there a suggestion of the likelihood of success in arriving at the presently claimed invention. As noted, Rocklage '744 does not disclose a method of distinguishing between reversibly injured tissue and irreversibly injured tissue, a claim limitation which cannot be ignored. Rocklage describes only a method for detecting ischemia. Ischemia is a decrease of blood supply which leads to an inadequate supply of oxygen where the blood supply is limited as would be appreciated by one of ordinary skill in the art.

Independent claim 96 is directed to a method of distinguishing viable myocardial tissue from necrotic (infarcated) tissue. As discussed at the interview ischemia leads to the damage of tissue to which the patient's blood supply has been affected. The extent of the tissue damage within a patient can vary such that the damage to some tissue is reversible, whereas the damage to other tissue is not. Claim 96 is limited to a method for distinguishing between these types of tissue following/during an ischemic event. Such a method is nowhere disclosed or suggested in Rocklage '744 as would be appreciated by one of ordinary skill in the art.

The contrast agents described in Rocklage '744, in particular the Dy-compounds described in the Examples of '744, are blood pool agents and are detected in the blood

supply by MRI as would be appreciated by one of ordinary skill in the art to which the invention pertains. As a result, the method described in Rocklage '744 can only be used to identify and/or monitor abnormal or modified blood flow. The method does not involve or allow for the detection of damaged tissue in accordance with the claims on appeal.

It was also pointed out at the interview that the manganese contrast agents of the claimed invention dissociate once they have been administered into the body and the resulting manganese ions are able to enter viable (i.e. repairable) myocardial cells via Ca^{2+} channels.

It was pointed out at the interview that claim 96 also requires that within a period of from 3 to 6 hours following administration of the Mn complex or salt to the body, the body is subjected to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and distinguishing viable myocardial tissue from infarcated tissue. The Examiner agree to further consider these points.

In view of the above comments, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,
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January 12, 2007